AR201-12680a

Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-

CAS No. 2530-83-8

Test Plan
Reduced Testing Rationale
Robust Summaries

July 20, 2000

Submitted to EPA under the HPV Challenge Program by:

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Test Plan

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Chemical	Physical-Chemical				
	Melting Point	Boiling Point	Vapor Pressure	Partition Coefficient	Water Solubility
2530-83-8 Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-[1]	NR[2]	A	A	NA[3]	NA[3]

Chemical	Environmental Fate			
	Photo-degradation	Stability in Water	Transport/ Distribution	Biodegradation
2530-83-8 Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-[1]	NA[3]	Test	NA[3]	A

Chemical	Ecotoxicity		
	Acute Toxicity to Fish	Acute Toxicity to Aquatic Plants (e.g., Algae)	Acute Toxicity to Aquatic Invertebrates (e.g., Daphnia)
2530-83-8 Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-[1]	A	A	A

Chemical	Toxicity					
	Acute Toxicity	Genetic Toxicity *In Vitro*	Genetic Toxicity *In Vivo*	Repeat Dose Toxicity	Repro-ductive Toxicity	Develop-mental Toxicity
2530-83-8 Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-[1]	A	A	A	A[4]	NA[3]	A[4]

[1] Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy- (CAS No. 2530-83-8) is also known, and will be referred to, as 3-(Trimethoxysilyl)propyl glycidol ether (TMSPGE) or 3-Glycidoxypropyltrimethoxysilane.

[2] Endpoint is not required because the melting point for this liquid is less 0°C. (a) Melting point <-70°C. Material Safety Data Sheet. CAS No. 2530-83-8. Union Carbide Chemicals and Plastics Company, Inc. Effective date 21 February 1991.

[3] Endpoints are not applicable because the chemical is hydrolytically unstable.

[4] As our experience and knowledge associated with the issues surrounding the testing of TMSPGE increased, it has become apparent that it is not stable by the oral route. Specifically, TMSPGE readily hydrolyzes to methanol and silanols (Note: methanol is included in the EPA HPV Challenge Program and the ICCA Global

Initiative on HPV Chemicals). pH has a significant effect on the rate of hydrolysis, and at pH 4, the hydrolysis is complete within 2.5 minutes. Slight changes in pH affect the rate of hydrolysis, which may result in administration of differing forms of the test article with each dosing. The hydrolysis rate is susceptible to the presence of trace acid and/or base. The lack of clinical signs of toxicity following acute or repeated dosing is likely related to the hydrolysis of TMSPGE and subsequent polymerization of the hydrolysis products, and thus, the lack of bioavailability.

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties
O	Other

Date Work Plan Available for Comment: (Q3, 2000)

Date Work Plan Complete: (quarter, year)

Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy-[1] Reduced Testing Rationale

(Difficult-to-Test Substance)
CAS No. 2530-83-8

Silicones Environmental, Health and Safety Council
July 20, 2000

Introduction

EPA has recognized that some chemicals in the HPV Challenge Program are difficult to test for a number of reasons for one or more endpoints. Sponsors are encouraged to follow appropriate SIDS guidance, where available, and develop a rational test plan with the necessary alternative test battery.

Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy- (CAS No. 2530-83-8), also known and herein referred to as 3-(trimethoxysilyl)propyl glycidol ether (TMSPGE), is listed as an HPV Challenge Program chemical. In this document, the Silicones Environmental, Health and Safety Council (SEHSC) reviews the reactive nature of TMSPGE, the exposure potential and manufacturing, and use of this glycidol ether to support its proposed difficult-to-test status and associated reduced testing rationale.

TMSPGE is a highly reactive chemical and is subject to rapid hydrolysis. At pH 4, TMSPGE is completely hydrolyzed in 2.5 minutes. The calculated half-lives for hydrolysis at various pH values are given in Table 1.[2]

Table 1. The calculated half-lives for hydrolysis of TMSPGE at 25 °C at various pH values.

pH	3	4	5	6	7	8	9	11
Half-life	3.0	30	5.0	49	4.0	45	4.6	2.7
Time unit	second	second	minute	minute	hour	minute	minute	second

[1] Silane, [3-(2,3-epoxypropoxy)propyl]trimethoxy- (CAS No. 2530-83-8) is also known, and will be referred to, as 3-(trimethoxysilyl)propyl glycidol ether (TMSPGE) or 3-Glycidoxypropyltrimethoxysilane.

[2] Pohl, E.R. and F.D. Osterholtz. 1985. Kinetics and mechanism of aqueous hydrolysis and condensation of alkyltrialkoxysilanes. *Polym. Sci. Technol.* 27:157-170.

These data will be confirmed by additional hydrolysis studies to be conducted as indicated in the test plan for this substance. Preliminary results indicate that the hydrolysis rate is susceptible to any traces of base and may be dependent on the concentration of buffer.

In analyzing the adequacy of the existing data, we have conducted a thoughtful, qualitative analysis, and have concluded that there are sufficient data, given the totality of what is known about this chemical, including human experience, that certain endpoints need not be tested. Note that, throughout the development of the test plan, we have incorporated consideration of animal welfare concerns and scientific principles.

Three technical factors have been identified during the conduct of repeated toxicity testing that makes HPV toxicological testing infeasible and inappropriate. These factors are (1) the polymerization of the test article in the stomach following oral exposure, (2) the necrotizing effect of the test article following dermal exposure, and (3) the lack of exposure via inhalation based on a very low saturated vapor concentration [12 parts per million (ppm)]. Furthermore, as stated in EPA's Part 870 Health Effects Test Guidelines[3], additional factors related to typical exposures in humans further limit the choice of route of administration. That is, *"The choice of the route of administration depends upon the physical and chemical characteristics of the test substance and the form typifying exposures in humans."* Systemic effects via inhalation are unlikely since hydrolysis occurs when TMSPGE contacts moist air in the environment or the lung if released during use. Moreover, as TMSPGE hydrolyzes, its saturated vapor concentration at ambient temperatures falls below 12 ppm, reducing the potential for inhalation exposure to any residual TMSPGE. TMSPGE hydrolysis results in highly cross-liked, high molecular weight polymers, which further reduces the potential for exposure. The oral route of exposure is impracticable not only because ingestion is not intended by humans, but also because the test article rapidly hydrolyzes and polymerizes under stomach pH conditions. The hydrolysis and polymerization half-lives are so short that the absorption of the test article would be insufficient due to polymerization of the hydrolyzed test article in the stomach. The doses of TMSPGE that would be selected for dermal exposures are expected to be so low as to be meaningless. Furthermore, hydrolysis after application on, or contact with, the skin, respectively, is very likely to occur. This results in the formation of high molecular weight polymers that, due to their size, are not capable of penetrating the skin barrier such that systemic bioavailability is excluded.

Background Information: TMSPGE Exposure Potential, Manufacturing and Commercial Applications

The number of individuals likely to be exposed to TMSPGE is small and the potential levels of TMSPGE to which these individuals may be exposed are extremely low, as explained below.

Exposure During the Manufacture of TMSPGE

The physical and chemical properties of TMSPGE minimize the potential for exposure to this substance during its manufacture. Because TMSPGE has a low vapor pressure (the saturated vapor concentration at ambient temperatures is approximately 12 ppm), there is little potential for inhalation exposure.

[3] http://www.epa.gov/docs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/

Monitoring studies of manufacturing workers and manufacturing areas where potential exposure would be greatest (i.e., filling and pouring operations) confirm that only low concentrations (time weighted average (TWA) of 0.63 ppm) of TMSPGE are present in the workplace atmosphere. The likelihood of forming aerosols is very low and would occur only if improper handling procedures are used.

TMSPGE is a moisture-reactive material that hydrolyzes rapidly (half-life of < 3 seconds to about 4 hours, depending on the aqueous solution pH and concentration of buffer). In the unlikely event of an accidental spill, TMSPGE could enter the environment through evaporation (limited by the very low saturated vapor concentration) or through direct contamination of surfaces, soil and surface waters. TMSPGE will react with the humidity in the air, moisture in the soil, or directly with the water of streams, lakes, and rivers. The rate of hydrolysis will depend upon the nature of the spill. If TMSPGE is in contact with large amounts of liquid water (either surface water or cleaning solutions), hydrolysis will occur very rapidly (minutes or hours). However, if TMSPGE is only in contact with low humidity air, hydrolysis can take considerably longer. Moreover, as TMSPGE hydrolyzes, its saturated vapor concentration at ambient temperatures falls to below 12 ppm, reducing the potential for inhalation exposure to any residual TMSPGE. Hydrolysis of TMSPGE results in highly cross-linked, high molecular weight polymers, further reducing the potential for exposure.

The number of workers that may be exposed to TMSPGE during its manufacture or handling is small. Given its chemical and physical properties, manufacturing and processing of TMSPGE occurs in enclosed equipment. Thus, the only workers that may be potentially exposed to TMSPGE are those who transfer materials from reaction vessels to shipping containers or who are exposed to the material during cleaning operations. As indicated previously, TMSPGE rapidly hydrolyzes and its saturated vapor concentration at ambient temperatures falls to below 12 ppm, reducing the potential for inhalation exposure to any residual TMSPGE.

Exposure to Workers During End-Use Applications

Worker exposure to TMSPGE is low during its use in applications. In many of its applications, TMSPGE is only a small component of the formulation or article and TMSPGE is chemically altered during use by hydrolysis, condensation with surfaces, or oligomerization. The dilution and reactions of TMSPGE reduce its bioavailability and apply with equal validity to all of the end-use applications of this material.

- **Component in Adhesives and Sealants**

TMSPGE is used most frequently in minor proportions as an adhesion promoter, coupling agent, or cross linker in adhesives, sealants, and encapsulants. Regardless of the particular adhesive or sealant with which it is mixed, TMSPGE is essentially never used at concentrations higher than ten percent. A level of one to two percent by weight is a commonly recommended as a "starting-point" in many formulations.

Although the precise function of TMSPGE varies based on the sealant or adhesive to which it is added, it usually becomes immobilized during use due to attachment to minerals or polymers in the adhesive or sealant. In silicone sealants, much of the TMSPGE reacts with hydroxyl groups on silanol end-capped silicone polymers, with hydroxyl on the surface of silica reinforcing fillers, or with trace water introduced on mineral filler surfaces. In instances where TMSPGE is used as an additive to improve the

adhesion of water-based or latex caulks and sealants, TMSPGE is polymerized and immobilized during the formulation process by reacting with water and mineral surfaces that are present in these products.

TMSPGE is sometimes used in solvent-based or 100 percent actives sealants, adhesives, and encapsulants. In these adhesive applications, TMSPGE becomes partially immobilized by reaction with the mineral fillers during the manufacturing process and reacts completely with the organic polymer during the curing process. Thus, when acting as a "coupling agent" or an "adhesion promoter" with any of the above adhesives or sealants, TMSPGE becomes covalently bonded to very high molecular weight polymers and minerals. This bonding to a high molecular weight material greatly reduces potential exposures.

- **Component of Coatings on Glass Fibers**

Another major application for TMSPGE is as a raw material in the manufacture of reinforcing glass fibers. During its use, TMSPGE is deliberately converted to the silanol form by hydrolyzing it in acidified water at concentrations usually below twenty percent by weight and typically between five and ten percent by weight. After the hydrolysis reaction is complete, the aqueous solutions of TMSPGE are further diluted with water and possibly other ingredients, such as emulsions of organic polymers, lubricants, surfactants, wetting agent, and other processing aids.

During application of these solutions, called sizes or finishes, to the glass fibers, there exists a potential for worker exposure to the hydrolysis products of TMSPGE. However, after the fibers are dried, the worker exposure is diminished greatly because these silanols are bonded directly to the glass fibers. This immobilization and chemical reactivity eliminates further end-user exposure to TMSPGE or its hydrolysis products. The final end-user takes these fibers and mixes them with organic resins to make composites.

- **Component of Foundry Additives**

Less than five percent of the production volume of TMSPGE is consumed as an additive to a foundry resin. In this use, a resin producer blends a phenolic or furan resin (polymer), which contains some water, with a small quantity of TMSPGE, typically between 0.01 and 0.1 percent. As the TMSPGE is blended, it hydrolyzes to silanol and oligomer forms because there is water in the resin. Moreover, TMSPGE reacts with the resin during curing reactions. Therefore, potential exposure to unreacted TMSPGE is minimal.

Exposure to General Population

SEHSC is unaware of any consumer use of this substance, and there is no exposure to the general population. Exposure of the public or the environment to these materials is possible only from accidental releases and would be of a short duration. Exposure via inhalation following such releases is unlikely based on a low saturated vapor concentration (12 ppm). As TMSPGE hydrolyzes, its saturated vapor concentration at ambient temperatures falls to below 12 ppm, further reducing the potential for inhalation exposure to any residual TMSPGE.

Matrix of SIDS Endpoints

In order to construct a matrix of SIDS endpoints for TMSPGE, the data on physicochemical properties, environmental fate and effects, and health effects must be collected and evaluated for adequacy. The

results of these activities are presented in Table 2, which provides a matrix of available and adequate data on TMSPGE.

Table 2

Matrix of Available and Adequate Data on TMSPGE	
Test ***Physicochemical Properties***	
Melting Point	√[4]
Vapor Pressure	√
Boiling Point	√
Partition Coefficient	-
Water Solubility	-
Hydrolysis	√
Photodegradation	-
Biodegradation	√
Environmental Transport	-
Test ***Ecotoxicity***	
Acute Fish	√
Acute Daphnid	√
Algae	√
Terrestrial	NA
Test ***Heath Effects***	
Acute Oral	√
Acute Inhalation	√
Acute Dermal	-
Repeated Dose	√[5]
Genotoxicity (*in vitro* -bacteria)	√
Genotoxicity (*in vitro* - nonbacterial)	√
Genotoxicity (*in vivo*)	√
Repro/Developmental	√[5]
(√) = Data available and considered adequate; (NA) = Not applicable due to chemical/physical properties; (-) No data available, or data considered inadequate	

[4] Melting Point <-70°C. Material Safety Data Sheet. CAS No. 2530-83-8. Union Carbide Chemicals and Plastics Company, Inc. Effective date 21 February 1991.

[5] As our experience and knowledge associated with the issues surrounding the testing of TMSPGE increased, it has become apparent that it is not stable by the oral route. A non-GLP study was conducted to examine the fate of TMSPGE following oral (gavage) exposure. This study showed that little or no absorption of test article appeared to have occurred. The lack of clinical signs of toxicity following acute or repeated dosing is likely related to the hydrolysis of TMSPGE and subsequent polymerization of the hydrolysis products, and thus, the lack of bioavailability. The recognition of the instability of TMSPGE precludes future testing of this material via the oral route.

Reduced Testing Rationale

EPA has recognized that some chemicals in the HPV Challenge Program are difficult to test for a number of reasons for one or more endpoints. Sponsors are encouraged to follow appropriate SIDS guidance, where available, and develop a rational test plan with the necessary alternative test battery.

TMSPGE is a highly reactive chemical and is subject to rapid hydrolysis in the presence of moisture. At pH 4, TMSPGE is hydrolyzed completely in 2.5 minutes; at pH 11 or 3, the half-life is about 3 seconds, and at pH 9 or 5, the half-life is about 5 minutes.[6] Slight variations in pH (for example, at pH 7 vs. 7.2) result in a change in the rate of hydrolysis; furthermore, the hydrolysis rate is susceptible to any traces of base and may be dependent on buffer concentration. This material is extremely difficult to handle during the conduct of toxicological or environmental testing. Exposure of the public or the environment to these materials is possible only from accidental releases and would be of a short duration. TMSPGE hydrolyzes rapidly to form silanols and methanol. These silanol solutions can form highly cross-linked, high molecular weight polymers when dried. These polymers are not biologically available due to their high molecular weight. Methanol, a byproduct of the hydrolysis reaction, is included separately under EPA's HPV Challenge Program and the ICCA Global Initiative on HPV Chemicals.

Concentrated solutions of silanols that are formed upon hydrolysis of TMSPGE will condense to oligomers or polymers. Many of these oligomers and polymers are insoluble in an aqueous solution and will precipitate out. In contrast to soluble polymers from other silanes, the polymers from TMSPGE (if the epoxy ring does not open) have limited water solubility. TMSPGE will form silanetriol, dimers, trimers, and oligomers. Viscosity and solubility of gastric solutions of TMSPGE will depend on the degree of condensation, number of silanol groups remaining, and the degree of epoxy ring opening. Epoxy rings react in acidic water to form diols, but the rate of ring-opening is much slower than the rate of silane hydrolysis. The diol form of TMSPGE has higher water solubility.

Infeasibility of Health and Environmental Testing of TMSPGE

Toxicology testing requires exposure to animals in a moisture-containing environment. For example, in inhalation testing, ambient air contains a significant level of moisture (generally 30-70%). In aquatic toxicity tests, the test environment is water-based. In these and other testing situations, TMSPGE will hydrolyze to form methanol and silanols. As stated previously, the EPA HPV Challenge Program and the ICCA Global Initiative on HPV Chemicals separately includes methanol.

In analyzing the adequacy of the existing data, we have conducted a thoughtful, qualitative analysis, and have concluded that there are sufficient data, given the totality of what is known about this chemical, including human experience, that certain endpoints need not be tested. Note that, throughout the development of the test plan, we have incorporated consideration of animal welfare concerns and scientific principles. On this basis, an alternative test battery is planned.

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[6] Pohl, E.R. and F.D. Osterholtz. 1985. Kinetics and mechanism of aqueous hydrolysis and condensation of alkyltrialkoxysilanes. *Polym. Sci. Technol.* 27:157-170.

Detailed studies will be conducted to evaluate the hydrolysis kinetics and rate of degradation. However, because the material is known to be hydrolytically unstable and rapidly generates methanol when added to water, endpoints such as octanol/water partition coefficient and water solubility are not appropriate, and will not be determined. Similarly, environmental fate properties, which are not appropriate due to the nature of the test article, include photodegradation and transport/distribution modeling. Biodegradation studies suggest that about 37 percent of the material is degraded after 28 days. However, these results reflect the degradation of methanol and not the parent material. Aquatic toxicity testing indicates that TMSPGE is practically non-toxic (EC_{50} > 100 ppm) to fish, invertebrates, and algae.

A technical infeasibility has been identified with the conduct of repeated dose mammalian toxicity testing due to (1) the polymerization of the test article in the stomach following oral exposure, (2) the irritating nature of the test article following dermal exposure, and (3) the lack of exposure via inhalation based on a very low vapor pressure (12 ppm). Details describing the issues associated with the use of each of these exposure routes follow.

- **Oral Exposure**

Ingestion of TMSPGE is not an intended route of exposure for humans. As stated in EPA's Part 870 Health Effects Test Guidelines,[7] *"The choice of the route of administration depends upon the physical and chemical characteristics of the test substance and the form typifying exposures in humans."* Further, as described previously in this document, TMSPGE readily hydrolyzes to methanol and silanols. pH has a significant effect on the rate of hydrolysis, and at pH 4, the hydrolysis is complete within 2.5 minutes. Slight changes in pH also affect the rate of hydrolysis, which may result in exposure to differing forms of the test article with each administration. Finally, the hydrolysis rate is susceptible to the presence of even traces of base and may be dependent on buffer concentration.

A non-GLP study was conducted to examine the fate of TMSPGE following gavage. Five fasted female Sprague-Dawley rats were dosed with 2000 mg/kg TMSPGE mixed with activate charcoal as a tracer. After 20 or 30 minutes the animals were sacrificed, and the stomachs and gastrointestinal tracts examined for presence of test article. The study was also repeated in the absence of the activated charcoal tracer. In all cases, the test article was found in the stomach contents or in the upper gastrointestinal tract, and was observed to have the consistency of thick mucous. In cases where the stomach contents included food, small waxy particles of test article were observed. Both the thick mucous and waxy particle forms of the test article observed in the stomach and upper gastrointestinal tract support the rapid polymerization of TMSPGE under oral (gavage) conditions, as the test article exists as a clear, water-like liquid. In either case, little or no absorption of test article appeared to have occurred. In contrast, there was no liquid present in the stomachs of animals gavaged with an equivalent dose of water and sacrificed after 30 minutes.[8]

The low order of acute or repeated dose toxicity associated with TMSPGE is attributed to the lack of bioavailability. The conduct of additional studies will not contribute to an additional understanding of the potential health effects of this material, and it is unnecessary to proceed with further testing involving animals. Additional information obtained through the repeated oral testing of TMSPGE would not be useful or relevant.

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[7] http://www.epa.gov/docs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/

[8] WIL Research. July 2000. Single Dose Study in Albino Rats. Study No. WIL-401001.

- **Dermal Exposure**

Application of small amounts of TMSPGE (0.01 mL) to the clipped skin of the rabbit belly uncovered for 24 hours resulted in moderate to marked capillary injection. In a preliminary study of the irritant potential from recurrent applications of TMSPGE to the skin of mice, a maximum concentration of TMSPGE of 25 percent in acetone was selected in order to avoid significant primary skin irritation over the lifetime of the animals.

A human patch test was conducted to determine whether TMSPGE was capable of causing skin irritation in humans under controlled conditions, and if so, to classify the material as a "primary" irritant on the basis of the observed clinical response. TMSPGE was applied to the infrascapular area of the back, under an occlusive patch at concentrations of 100, 75, 50, 25, 10, and 1% (in methanol) for a period of 48-hours. TMSPGE was very irritating under the conditions employed in this study, with initial reactions (after 48 and 74 hours) characterized by redness, scaling and crusting, edema, and hyperpigmentation. Definite irritation was observed at 100, 75, 50, and 25% concentrations, while the irritation was not considered clinically significant at concentrations of 1 and 10%.

As stated in EPA and OECD test guidance, the highest dose selected in a repeated dose study should result in toxic effects. The dermal studies conducted with TMSPGE suggest that a sufficiently high dose of TMSPGE could not be applied during a repeated dose study without significant skin irritation.

The doses of TMSPGE that would be selected for dermal exposures are expected to be so low as to be meaningless. Furthermore, hydrolysis after application on, or contact with, the skin, respectively, is very likely to occur. This results in the formation of high molecular weight polymers that, due to their size, are not capable of penetrating the skin barrier such at systemic bioavailability is excluded. The conduct of repeated dose dermal studies will not contribute to an additional understanding of the potential health effects of this material, and would serve as an unnecessary use of laboratory animals.

- **Inhalation Exposure**

The physical and chemical properties of TMSPGE minimize the potential for exposure to this substance during its manufacture. Because TMSPGE has a low vapor pressure (the saturated vapor concentration at ambient temperatures is approximately 12 ppm), there is little potential for inhalation exposure. As TMSPGE hydrolyzes, its saturated vapor concentration at ambient temperatures falls to below 12 ppm, further reducing the potential for inhalation exposure to any residual TMSPGE.

Monitoring studies of manufacturing workers and manufacturing areas where potential exposure would be greatest, i.e., filling and pouring operations, confirm that only low concentrations (TWA of 0.63 ppm) of TMSPGE are present in the workplace atmosphere. Exposure of the public or the environment to these materials is possible only from accidental releases and would be of a short duration.

Repeated dose studies, including additional reproductive and developmental endpoints, will not be included in the HPV test plan for TMSPGE because of the rapid hydrolysis following contact with moisture, and the production of biologically unavailable high molecular weight polymer. The conduct of inhalation toxicity studies will not contribute to an additional understanding of the potential health effects of this material, and would serve as an unnecessary use of laboratory animals.